IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Maria Adele Pacciarini, et al.	**Examiner:**	Ganapathy Krishnan
Serial No.:	09/786,998	**Art Unit:**	1623
Filed:	June 14, 2001	**Docket:**	17815
For:	USE OF AN ANTHRACYCLINE DERIVATIVE FOR THE TREATMENT OF A LIVER TUMOR		
Dated:	March 28, 2011		

Confirmation No.: 1122

Commissioner for Patents
Washington, DC 20231

REASONS FOR PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicants submit the ensuing in support of their Pre-Appeal Brief Request for Review.

Claims 18-23 and 25-37 pend. All were finally rejected under 35 U.S.C. §103 by Official Action dated October 27, 2010.

The primary reference is Bakker et al. (*British Journal of Cancer*, 1998, Jan., 77(1), 139-146. (Hereafter "Bakker")

The secondary references include: Horiguhi et al. (*Cancer Chemother. Pharmacol.* 1992, 31 (Suppl I) S60-S64; Kuhl et al. (*Cancer Chemother. Pharmacol.* 1993, 33, 10-16); Gorbunova

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CERTIFICATION OF ELECTRONIC FILING

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Dated: March 28, 2011

Peter I. Bernstein

(*Intrahepatic Arterial Infusion Chemotherapy for Primary and Metastatic Cancer of the Liver*, 1990); and Brem et al. US 5626862. (Hereafter, collectively, the "Secondary References")

I. The Invention

The application contains claims directed to a method of treating human liver cancer. The method comprises intrahepatic administration of methoxymorpholino doxorubicin (MMDX) under specified dosage regimens. Other claims include a method of reducing systemic exposure to MMDX and a pharmaceutical composition comprising MMDX.

II. Clear Error

The rejection is improper because the primary reference on which the entire rejection rests, Bakker, openly reports dissuasive results for MMDX in multiple other types of malignancies such that one would not be motivated to consider it for liver cancer in the first place, let alone have any reasonable expectation of success in that milieu.

The primary reference, on its own terms, unambiguously teaches away from MMDX. These unambiguous teachings were improperly considered and effectively dismissed by the Official Action in favor of unsubstantiated argument. Clear error is involved meriting a reversal of the rejection.

III. Discussion

A. The Claims

Of Claims 18-23 and 25-37, the following are independent: 18, 19, 25, 31, 32, 33 and 34. Claims 18, 25, 31 and 32 are to a method of treating human liver cancer. Claims 19 and 33 are to a method of reducing MMDX systemic exposure in a patient suffering from a liver cancer. A feature common to all method claims is the intrahepatic administration of MMDX, in a therapeutic amount. Depending on the claim, the MMDX is administered as an infusion from about 15 minutes to about 30 minutes every 4 weeks, or as a 5-10 minute bolus every 8 weeks.

Claim 34 is a pharmaceutical composition for the treatment of a human liver cancer by intrahepatic administration via injection into the hepatic artery. The composition comprises MMDX in an amount sufficient to provide a dosage of about 100 mcg/m2 to about 1000 mcg/m2; and a pharmaceutically acceptable agent which remains selectively in a liver tumor after injection, *e.g.* an iodized oil.

B. Bakker Teaches Away

Bakker reports results using MMDX in patients with lung cancer, head and neck cancer, renal cancer, colorectal cancer, cancer of the cervix, and adenocarcinoma of unknown provenance. The results are related as follows: for lung and renal cancer, the response rate was "disappointingly low" the article concluding that:

"MMDX can be considered as ineffective."

For head and neck cancer, cervical cancer and the adenocarcimona, the efficacy of MMDX was deemed as "yet unclear" because of low patient numbers.

See Bakker, DISCUSSION, p. 144, right hand column, 3rd full paragraph ("In the present study…").

Bakker does not disclose treating a human liver cancer with MMDX.

Bakker does not disclose intrahepatic administration of MMDX.

Both omissions are conceded by the Official Action.

Despite the altogether discouraging outcomes announced by Bakker for MMDX over a plethora of different cancers, the Official Action contends that this "would not dissuade one of skill in the art from using it for the treatment of lung cancer." Official Action, October 27, 2010, p. 8. The Official Action defends this by pointing to alleged high tissue distribution and leukocyte levels of MMDX, which, we are told, make it a "still a very interesting compound in potentially more sensitive tumor types." *Id.*

This conclusion is *ipse dixit*. It ignores the actual teachings of Bakker which, by any objective measure, would be read as having a chilling effect on motivation. The notion that tissue distribution and leukocyte levels would nullify the decidedly negative outcomes in Bakker, or somehow provide a renewed motivation in view of the somber results otherwise reported, is unsubstantiated. Where is it of record that one in the art would consider tissue distribution as paramount to essentially failed results? Where is it of record that such considerations have any currency in regard to lung cancer? And where is it of record that, based on same, one would have a reasonable expectation of success with lung cancer?

Rather than take the discrepant teachings of Bakker as they are, the Official Action insists on arbitrarily forcing them together using nothing more than bare assertions to reach the desired end result: that one in the art would be properly motivated, by reading Bakker, to apply MMDX to lung cancer, and that one would objectively expect success. Applicants are hard pressed to find a more textbook example of a teaching away than Bakker. Indeed, Bakker is prototypical of art in that teaches away in a pharmaceutical context. Nothing of record, by way of evidence or well-founded argument detracts from this.

Bakker does <u>not</u> reasonably motivate one to use MMDX in lung cancer. Quite the opposite. Nor does it envision the benefits unexpectedly achieved by the invention. Contrary to the woeful expectations derived from Bakker, Applicants have found that MMDX, when administered intrahepatically, is unexpectedly useful in treating human liver cancer. See the activity and tumor response data at pages 13-14 of the specification and the improved systemic toxicity data on pages 12-13. See also page 2, lines 6 to 19 of the specification finding that MMDX is highly potent when administered *in vivo* and its cytotoxic activity is increased *in vitro* in the presence of liver microsomes, which is indicative of MMDX transforming to highly cytotoxic metabolites. MMDX

is converted *in vivo* into the corresponding 13-dihydro derivative, having an activity and a toxicity that are 10 fold higher than those of the parent compound.

Bakker not only fails to foresee this, it actively steers one away from MMDX.

See Amendment and Remarks, August 9th 2010, pages 6-8 whereat the foregoing is further discussed.

C. The Secondary References

Suffice it to say, none relate to MMDX with liver cancer and intrahepatic administration. Applicants refer to, and incorporate herein by reference, their comments in regard to these references as stated in the Amendment and Remarks, August 9, 2010, pages 8-11.

IV. Conclusion

The teaching away by Bakker is unequivocal and was improperly dismissed by the Official Action. The removal of Bakker on this basis usurps the rejection and withdrawal of same is in order. Applicants submit that the claims are non-obvious and patentable in all respects, and request favorable consideration on this pre-appeal brief and passage of the application to issuance.

Respectfully submitted,

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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)	
17815	

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Application Number	Filed
09/786,998	June 14, 2001

First Named Inventor: Maria Adele Pacciarini, et al.

Art Unit	Examiner
1623	Ganapathy Krishnan

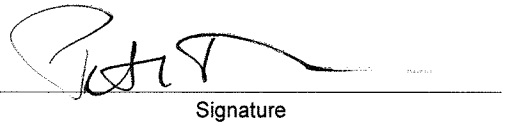
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number **43,497**
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____



Signature

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Telephone number

March 28, 2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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